CFH gene

complement factor H

Normal Function

The *CFH* gene provides instructions for making a protein called complement factor H. This protein helps regulate a part of the body's immune response known as the complement system. The complement system is a group of proteins that work together to destroy foreign invaders (such as bacteria and viruses), trigger an inflammatory response, and remove debris from cells and tissues. This system must be carefully regulated so it targets only unwanted materials and does not damage the body's healthy cells. Complement factor H, together with several related proteins, protects healthy cells by preventing the complement system from being turned on (activated) when it is not needed.

Health Conditions Related to Genetic Changes

age-related macular degeneration

Several variants in and near the *CFH* gene have been identified in people with age-related macular degeneration, an eye disease that is a common cause of vision loss in older adults. The Tyr402His polymorphism (described above) appears to be associated with an increased risk of this condition. People who carry one copy of this polymorphism in each cell have a 2.5-fold increased risk of developing age-related macular degeneration compared to people who do not have the polymorphism, and people who carry two copies of the polymorphism have a six-fold increased risk. However, most people with these variants never develop the disorder.

Age-related macular degeneration is characterized by the buildup of yellowish deposits called drusen underneath the light-sensitive tissue at the back of the eye (the retina). This buildup, together with other changes in the retina, leads to a progressive loss of central vision in late adulthood. Researchers suspect that changes in the *CFH* gene alter the production of complement factor H, although it is unclear how the abnormal protein is related to the buildup of drusen and progressive vision loss. Age-related macular degeneration is a complex condition that likely results from a combination of genetic and environmental factors.

atypical hemolytic-uremic syndrome

More than 100 mutations in the *CFH* gene have been identified in people with atypical hemolytic-uremic syndrome, a condition that causes abnormal blood clots

(thrombi) to form in small blood vessels in the kidneys. Mutations in this gene increase the risk of a severe form of the disorder that usually appears early in life.

Most *CFH* gene mutations associated with atypical hemolytic-uremic syndrome affect a region of the complement factor H protein known as the C-terminal domain. These mutations result in the production of an abnormal or nonfunctional version of the protein. The resulting shortage of complement factor H can lead to uncontrolled activation of the complement system on the surface of cells. The overactive system attacks cells known as endothelial cells that line small blood vessels in the kidneys. Damage to these cells often leads to kidney failure and ESRD.

Although genetic changes increase the risk of atypical hemolytic-uremic syndrome, studies suggest that they are often not sufficient to cause the disease. In people with *CFH* gene mutations, the signs and symptoms of the disorder may be triggered by factors such as certain medications (such as anti-cancer drugs), chronic diseases, viral or bacterial infections, cancers, organ transplantation, or pregnancy.

C3 glomerulopathy

Several mutations in the *CFH* gene have been found to cause a rare form of kidney disease called C3 glomerulopathy. This disorder damages the kidneys and can lead to end-stage renal disease (ESRD), a life-threatening condition that prevents the kidneys from filtering fluids and waste products from the body effectively.

Most of the *CFH* gene mutations that cause C3 glomerulopathy change single protein building blocks (amino acids) in complement factor H. These mutations prevent cells from making this protein or lead to the production of a nonfunctional version of the protein. The resulting shortage (deficiency) of complement factor H overactivates the complement system, which damages structures called glomeruli in the kidneys. These structures are clusters of tiny blood vessels that help filter waste products from the blood. Damage to glomeruli prevents the kidneys from filtering waste products normally and can lead to ESRD.

Several other changes involving the *CFH* gene do not cause C3 glomerulopathy directly but appear to increase the likelihood of developing the disorder. The best-studied of these gene variations (polymorphisms) is written as Tyr402His or Y402H. Complement factor H usually has the amino acid tyrosine (Tyr/Y) at position 402, but sometimes it has the amino acid histidine (His/H) instead. People with C3 glomerulopathy are more likely than people in the general population to have histidine at this position. The version of complement factor H with histidine at position 402 is less effective at regulating the complement system on cell surfaces than the version with tyrosine at position 402, which may help explain the increased disease risk.

other disorders

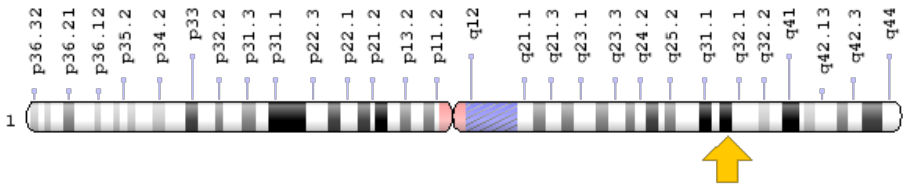
Variations in the *CFH* gene, including the Tyr402His polymorphism (described above), have also been associated with an eye disease called basal laminar drusen

(BLD). This condition is characterized by a buildup of drusen beneath the retina starting in early adulthood (in contrast to age-related macular degeneration, which begins later in life). It is unclear how changes in complement factor H are related to the accumulation of drusen in people with BLD. A combination of genetic and environmental factors likely determines the risk of developing this complex disorder.

Chromosomal Location

Cytogenetic Location: 1q31.3, which is the long (q) arm of chromosome 1 at position 31.3

Molecular Location: base pairs 196,651,878 to 196,747,504 on chromosome 1 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- age-related maculopathy susceptibility 1
- AHUS1
- ARMD4
- ARMS1
- beta-1-H-globulin
- beta-1H
- C3b inactivator accelerator
- CFAH_HUMAN
- CFHL3
- factor H
- factor H-like 1
- FH
- FHL1

- H factor 1 (complement)
- H factor 2 (complement)
- HF
- HF1
- HF2
- HUS
- MGC88246

Additional Information & Resources

Educational Resources

- Immunobiology (fifth edition, 2001): The Complement System and Innate Immunity
  https://www.ncbi.nlm.nih.gov/books/NBK27100/
- The Merck Manual for Healthcare Professionals: Complement System
  http://www.merckmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/complement-system.html?qt=&sc=&alt=
- Webvision: The Organization of the Retina and Visual System (2008): Molecular genetics of AMD
  https://www.ncbi.nlm.nih.gov/books/NBK27323/#maculardegen.Molecular_genetics_of_AMD

GeneReviews

- Dense Deposit Disease / Membranoproliferative Glomerulonephritis Type II
  https://www.ncbi.nlm.nih.gov/books/NBK1425
- Genetic Atypical Hemolytic-Uremic Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1367

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28CFH%5BTI%5D%29+OR+%28complement+factor+H%5BTI%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- BASAL LAMINAR DRUSEN
  http://omim.org/entry/126700
- COMPLEMENT FACTOR H
  http://omim.org/entry/134370

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_CFH.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=CFH%5Bgene%5D
- FH aHUS Mutation Database
  http://www.fh-hus.org/
- HGNC Gene Family: Complement system
  http://www.genenames.org/cgi-bin/genefamilies/set/492
- HGNC Gene Family: Sushi domain containing
  http://www.genenames.org/cgi-bin/genefamilies/set/1179
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=4883
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/3075
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  http://www.uniprot.org/uniprot/P08603

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Reviewed: December 2015
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
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